

Methyldopa in the Treatment of Hypertension*

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SINCE the initial communication of Oates et al¹ reporting that methyldopa lowered blood pressure in hypertensive patients additional studies have attested to the efficacy of this drug as an antihypertensive agent.²⁻⁷ Over the past 2½ years methyldopa (Aldomet®) has been utilized in this clinic usually in conjunction with sulfonamide saluretic agents in the long-term treatment of hypertensive outpatients. The drug was compared with guanethidine in 13 patients for periods averaging 6 months on each agent. In addition, adverse hepatic effects of methyldopa have been documented.

Materials and Methods

During the period of study 33 patients were treated in the hypertension clinic of the Mt. Alto Veterans Administration Hospital with methyldopa. Twelve patients had severe hypertension with 4 in the malignant phase, 19 with moderate hypertension, and 2 with mild hypertension.‡ The mean age was 45 years, and 25 of the group were Negroes. Only 3 patients exhibited normal electrocardiograms, the majority showing left ventricular hypertrophy. Twelve patients had blood urea nitrogen levels prior to therapy in excess of 25 mg. per 100 ml. of blood.

The interval between clinic visits averaged 2.5 weeks. At each clinic visit blood pressure recordings in the supine, sitting and erect positions were taken by a physician. Methyldopa was administered in divided doses 3 times daily. Doses

were adjusted at each clinic visit in order to obtain optimal blood pressure control within the range of tolerable side-effects. The sulfonamide diuretics which were used were either hydrochlorothiazide, 50 mg. twice daily, or chlor-thalidone, 100 mg. once daily.

Bromsulfalein (BSP), serum alkaline phosphatase, serum glutamic oxaloacetic transaminase (SGOT), and blood urea nitrogen (BUN) determinations were done after the patient had been instructed to fast overnight and omit breakfast. The amount of BSP retention was determined according to a modified method of Greene. Alkaline phosphatase was done by the method of Bodansky. SGOT was determined by a modified Reitman-Frankel method utilizing Dade® reagents, and the BUN was estimated with the Technicon® auto-analyzer.

Results

Effectiveness of therapy. Blood pressure changes in only 24 patients will be discussed, since information regarding the percentage change in blood pressure was not pertinent for 4 patients whose methyldopa was discontinued because of side-effects and for 5 patients who were transferred directly from guanethidine to methyldopa without an intervening control period.

Twelve of the 24 patients either became normotensive or had average mean blood pressures readings that were more than 20 per cent lower than the pretreatment mean pressures in both the supine and erect positions.¶ An additional 4 patients exhibited average mean blood pressures during the treatment period that were lower than their pretreatment levels by 20 per cent or more in the erect but not in the supine position. The

§ Mean blood pressure = diastolic blood pressure + ⅓ pulse pressure.

¶ Detailed tabular data on individual cases can be obtained by writing to the authors.

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‡ In the hypertensive grading of patients we utilized the criteria of the Veterans Administration Cooperative Study on Antihypertensive Agents, published in "A double-blind control study of antihypertensive agents," Arch. Int. Med., 1960, 106, 81.

average duration of therapy in these 16 patients was 40 weeks (range 13 to 96 weeks). The average dose of methyldopa was 1,365 mg. (range 540–2,375 mg.) per day. Fourteen of the 16 received saluretic agents concurrently.

The remaining 8 patients did not demonstrate reductions in their average blood pressures during the treatment period that were greater than 10 per cent of their pretreatment values. The average maximum dose of methyldopa in these patients was 1,906 mg. (range 1,750–3,000 mg.) per day. Seven of the 8 were treated concurrently with oral saluretic agents.

Tolerance. The records of 10 patients who were maintained with decreases of 20 per cent or more in mean blood pressure in the erect position were evaluated at 6 weeks, 3 months, and at the end of therapy. Dosage and blood pressure levels at intervals as close as possible to these periods were tabulated. Three of the 10 patients evidenced manifestations of tolerance (table 1). The

Transient symptoms suggesting orthostatic hypotension were noted in 20 of the 33 patients. For the most part these symptoms consisted only of mild dizziness on arising in the morning, but 3 patients experienced syncope which did not recur when dosage was reduced.

Four patients complained of diminished sexual drive after beginning methyldopa. In 1 case reduction in dosage sufficed to restore potency. In another patient the addition of a placebo without reduction in the dose of methyldopa led to restoration of normal potency. In the 2 remaining patients the complaint continued after their treatment was changed. It is, therefore, unlikely that the impotence was related to methyldopa in 3 of the 4 patients.

Four patients volunteered that they were having frequent dreams which seemed to be related to therapy. The dreams ceased, however, despite continuation of treatment. Four patients complained of "tenseness" and nervousness while

TABLE 1: Tolerance to Alpha Methyldopa

	Duration of Treatment								
	6 weeks			3 months			Final*		
	Blood Pressure (mm. Hg)		Daily Dose Alpha Methyldopa (mg.)	Blood Pressure (mm. Hg)		Daily Dose Alpha Methyldopa (mg.)	Blood Pressure (mm. Hg)		Daily Dose Alpha Methyldopa (mg.)
	Supine	Standing		Supine	Standing		Supine	Standing	
Tolerant patients (3)	157/103	159/112	1,333	173/113	163/116	1,500	165/114	170/114	2,450
Nontolerant patients (7)	145/96	131/95	1,000	147/99	140/105	1,214	133/96	118/88	1,321

* Average duration of treatment for tolerant patients, 6 months; for nontolerant patients, 12 months.

average daily dose of these patients at 6 weeks was 1,333 mg. and at 6 months 2,450 mg., all of the patients being treated throughout with saluretic agents. The blood pressure was slightly higher at 6 months despite the higher doses. In the remaining 7 patients the average daily dose was 1,000 mg. at 6 weeks and 1,321 mg. at 12 months with the average blood pressure lower at the 12-month interval. Five of these 7 patients were treated concurrently with saluretic agents throughout the entire period.

Side-effects. Side-effects were minimal. Drowsiness at the initiation of treatment was noted in most patients. It usually disappeared after several days on a given dose to recur again for a few days if the dose was increased. One patient, however, experienced persistent drowsiness over the course of 6 months, with the result that his employer complained that the patient was constantly falling asleep at his desk.

taking methyldopa. Other complaints less frequently encountered were dry mouth in 2 cases, headaches in 2, and constipation in 1. These minor subjective complaints were not necessarily related to the use of the drug.

Side-effects necessitating discontinuation of methyldopa occurred in only 3 instances. In 1, referred to above, persistent drowsiness ceased when the patient's therapy was changed to guanethidine. A second patient complained of vomiting and headaches which came on approximately 20 minutes after taking his medications. These symptoms recurred on 2 separate trials, and the patient refused further treatment with the drug. One other patient developed a macular, pruritic skin eruption after 4 weeks of methyldopa therapy. The rash cleared completely within 2 weeks of discontinuing treatment, and a second trial of the drug was not attempted.

Drug reactions. Fever and alterations in hepatic function tests associated with methyldopa administration have been reported in the literature.^{3, 5, 7, 8, 9} In the present series of 33 patients 2 cases of chills occurred and each was associated with alterations in liver function tests but without jaundice. Liver biopsy was obtained at the height of the illness in 1 of these patients (D.M.) and showed changes consistent with mild hepatitis due to drug reaction. Retesting with methyldopa was accomplished 9 months later at a time when all tests of liver function had returned to normal. The same alterations in serum glutamic oxaloacetic transaminase levels, cephalin flocculation tests, and bromsulfalein retention that had been present in the initial illness recurred on retesting.

The second patient, W.P., experienced the onset of chills 13 weeks after initiation of therapy at a time when he was receiving 2,250 mg. methyldopa per day, chlorthalidone, and hydrochlorothiazide. A mild elevation in the serum glutamic oxaloacetic transaminase level to 90 units and a bromsulfalein retention of 8 per cent were noted at this time. The transaminase level fell to 61 units in spite of continued administration of the drug. Retesting with $\frac{1}{2}$ the previously administered dosage of methyldopa following a 3-month cessation did not cause a recurrence of the chills, but the transaminase level rose from an initial level of 8 to 61 units at the end of the month. Bromsulfalein retention was essentially unchanged, falling during this month from 7.7 to 5.7 per cent.

One case of jaundice occurred in a patient who was known to be alcoholic. The acute onset of severe icterus was noted after he had taken methyldopa for 10 weeks in a dose of 750 mg. per day together with chlorthalidone, 100 mg. per day. Liver biopsy at the time of the acute illness showed florid cirrhosis. Retesting with methyldopa was accomplished $3\frac{1}{2}$ months later, the patient receiving 750 mg. daily for 6 weeks. There was no recurrence of jaundice during this time. Tests of hepatic function, performed during the sixth week, did not reveal any alteration from the slightly abnormal values obtained prior to retesting. No other symptoms or physical signs of hepatic disease were encountered in the present series.

Fifteen patients who had been taking methyldopa continuously had normal bromsulfalein retention, serum alkaline phosphatase levels, and serum glutamic oxaloacetic transaminase levels after an average period of 10.7 months (range 5

weeks to 17 months). The mean dose was 1,535 mg. (range 750–2,750 mg.) per day at the time the determinations were done. Two patients who died of renal failure during the course of this study did not show evidence of hepatic disease in gross or microscopic postmortem examinations of their livers.

Comparison with guanethidine.* Thirteen patients were treated with guanethidine and saluretic agents for sufficient periods of time to allow comparison with their response to methyldopa plus saluretic agents. The average duration of treatment with guanethidine was 30 weeks (range 3 to 94 weeks) and 25 weeks with methyldopa (range 10 to 57 weeks). The average blood pressure on guanethidine therapy was 166/109 mm. Hg supine and 139/100 mm. Hg in the erect position. The average supine blood pressure during methyldopa was 166/112 mm. Hg while the average erect blood pressure was 151/109 mm. Hg. The difference in mean orthostatic blood pressure levels on the 2 drugs was significant ($P < .02$). Twelve of the 13 patients received saluretic agents concurrently with both drugs while the remaining patient did not. The average daily dose of guanethidine was 32 mg. (range 12.5–69 mg.) taken once daily, and 1,610 mg. of methyldopa (range 1,125–2,250 mg.) taken in 3 divided doses.

Two of the above patients were transferred from methyldopa to guanethidine because of failure to respond significantly to large doses of the former. Seven other patients in the comparative series were receiving daily doses of methyldopa of 2,000 mg. or more at the time of transfer. On guanethidine, all of these patients were maintained with lower orthostatic blood pressures and in 4 with lower supine blood pressures as well. Four of these 9 patients were classified as severe hypertensive patients and 5 as moderate. Eight of the above were treated with saluretic agents on both regimens and 1 was not. Another patient was transferred to guanethidine after his blood pressure rose to 230/150 mm. Hg with severe daily headaches and weight loss of 9 pounds which occurred while he was taking methyldopa plus chlorthalidone. His blood pressure has since been maintained for over 1 year at average levels of 156/102 mm. Hg. supine and 128/91 mm. Hg erect with guanethidine plus a saluretic agent.

One patient with malignant hypertension who

* Ismelin®, a product of Ciba Pharmaceutical Company, Summit, New Jersey.

had manifested erratic control while taking guanethidine with hydrochlorothiazide for 27 weeks was transferred to methyldopa and chlor-thalidone. He maintained lower blood pressure levels during 18 weeks of treatment with the latter drug in an average daily dose of 2,000 mg. Higher blood pressures then recurred in spite of increasing doses. The blood urea nitrogen level had been 61 mg. per 100 ml. at the beginning of methyldopa therapy. Because of his mental confusion it is not certain that he took his pills correctly during this period. He subsequently died in renal failure. The 2 remaining patients in the series, both with moderate hypertension, maintained equally good control with either methyldopa or guanethidine.

Symptoms of orthostatic hypotension were more frequent and of greater severity while the patients were taking guanethidine. However, in no case was it necessary to discontinue treatment with guanethidine because of orthostatic hypotension; brief discontinuance and subsequent reduction of dosage were sufficient to alleviate the problem.

Seven of the 13 patients developed failure of ejaculation while taking guanethidine. In no case, however, was guanethidine discontinued because of this side-effect although the patients were informed that guanethidine was the causative agent. Only 1 of the 13 patients complained of any change in sexual function while taking methyldopa. This consisted of transitory impotence responding to a brief reduction in dosage. In spite of the side-effects noted above, none of the 13 patients expressed a preference for methyldopa over guanethidine. Two patients had occasional episodes of diarrhea while taking guanethidine whereas none complained of bowel disturbances with methyldopa.

Blood urea nitrogen levels were taken serially in 10 patients prior to and after completion of at least several months on each type of therapy. Excluding the patient who died in renal failure the average blood urea nitrogen level was 32 mg. per cent during methyldopa treatment as compared to 36 mg. per cent during treatment with guanethidine. The difference was not statistically significant and could be accounted for entirely by increase in blood urea nitrogen in 2 azotemic patients whose diastolic blood pressure levels in the erect position were 18 and 25 mm. Hg lower, respectively, during the guanethidine treatment period. In 1 of these patients a reduction in guanethidine dosage with consequent higher orthostatic blood pressures resulted in lower levels of blood urea nitrogen.

Comments

In the present study methyldopa in conjunction with oral diuretics proved effective in maintaining significant decreases in blood pressure in 16 of 24 patients. The use of saluretic agents seems indicated in view of the potentiation of action of methyldopa noted by ourselves as well as others.^{2, 3, 6, 7, 10, 11} Furthermore, problems of fluid retention noted occasionally on administration of methyldopa^{2, 7, 12} were obviated. Dollery and Harington² used methyldopa alone in doses up to 4.0 Gm. daily. Seven of 59 patients failed to respond. Cannon et al⁴ employed doses up to 8.0 Gm. per day and reported that 31 of 33 patients had a significant response. Onesti et al¹⁰ administered up to 2.8 Gm. per day and found that 13 of 24 patients obtained a significant anti-hypertensive response in the erect position; when hydrochlorothiazide was added in 7 nonresponders, 6 of these obtained a significant fall in blood pressure.

Tolerance to methyldopa has been noted by other investigators. Cannon et al⁴ noted that the dosage requirement of most patients increased somewhat after they were discharged from the hospital. Two of their 33 patients required discontinuation of methyldopa because of tolerance after 7 and 11 months, respectively. Dollery and Harington² noted that some increase in dosage was often necessary on the early outpatient visits after patients were discharged from the hospital. They also observed that a small number of their patients continued to require increasing dosages during prolonged treatment. Bayliss and Harvey-Smith¹² noted tolerance in 4 of their 20 cases so that doses of 3 Gm. or more per day were no longer effective. Daley and Evans¹³ noted significant tolerance in 2 of 20 patients. Smirk⁶ reported that increased doses were required to maintain the initial blood pressure falls in 6 of 14 patients. In 2 of these patients the increases were nearly 3-fold. In the present study it was found that while 3 of 10 patients manifested tolerance, requiring an average dose at 6 months that was nearly double the average dose at 6 weeks, the remaining 7 patients did not manifest tolerance after an average of 12 months of continuous treatment.

Drug reactions to methyldopa were first noted by Gillespie and co-workers.³ They reported 2 patients who developed fever within 2 weeks after the initiation of treatment with racemic methyldopa. Discontinuance of medication was associated with cessation of fever in both patients. On readministration of the drug, fever

recurred in 1 patient within 3 days. In the second patient fever did not recur with readministration, but elevations of serum alkaline phosphatase, transaminase and bilirubin levels similar to those that had been present with fever recurred within 2 days. Leonard et al⁸ reported 3 patients in whom febrile reactions occurred within 3 weeks of initiation of treatment. Methyldopa was readministered to 2 of these patients with reproduction of the fever. Sheps et al⁹ reported that fever occurred within 3 weeks of initiation of methyldopa in one of his patients and was associated with an elevated serum glutamic oxaloacetic transaminase level. The latter became normal 10 days after discontinuation of the drug. Retesting was not accomplished in this case. One brief note of the results of liver biopsy in another patient has been recorded.¹⁴ The liver became normal with discontinuation of methyldopa in this patient, but it is not stated whether retesting was undertaken.

The patient with hepatic injury in the present series represents the first reported case demonstrating hepatic changes by biopsy during the acute illness and recurrence of alterations of hepatic function tests when methyldopa was readministered. Several points are, therefore, of interest. The alterations present in the biopsy specimen were consistent with a hypersensitivity reaction with spotty necrosis but were not typical of "allergic cholangiolitis" with bile stasis¹⁵ as seen with chlorpromazine. The tests that were most useful in following the hepatic injury were the serum glutamic oxaloacetic transaminase, the cephalin flocculation test, and bromsulfalein retention. Elevation of the serum glutamic oxaloacetic transaminase level and a change in cephalin flocculation did not occur until 9 days after the start of retesting and persisted for at least 2 weeks after methyldopa was discontinued.

Review of the literature indicates that fever and alteration of hepatic function tests are infrequent complications of the use of methyldopa. No case of death or permanent alteration of hepatic function has been reported. It appears that hepatic injury induced by methyldopa requires some type of individual hypersensitivity to the drug and is reversible with discontinuation of the drug.

Most investigators have noted that methyldopa produces less orthostatic hypotension than does guanethidine. The results in the 13 cases reported above in which guanethidine and methyldopa were compared is consistent with this impression. In reviewing the literature, average supine and erect blood pressures of 62 patients

treated with methyldopa alone, reported in 5 articles,^{5, 10, 11, 16, 17} were 159/95 mm. Hg and 141/91 mm. Hg, respectively. Average supine and erect blood pressures of 62 patients who were treated with guanethidine alone, reported in 5 different articles,¹⁸⁻²² were 169/103 mm. Hg and 134/90 mm. Hg, respectively. Tests for statistical significance were not attempted for obvious reasons, but the finding of lower supine pressures with methyldopa when orthostatic diastolic pressures were equivalent tends to substantiate a widely held clinical impression.

In spite of the higher incidence of side-effects while taking guanethidine, patients continued to take their medications and none requested a resumption of methyldopa. Many patients preferred the small number of tablets and once daily administration associated with guanethidine. The shorter onset and effective duration of action of methyldopa were occasionally found to constitute a practical advantage. Initiation of effective therapy can be more rapid, and orthostatic hypotension, if it occurs, can be eliminated more rapidly through a reduction in dosage.

Methyldopa was not compared with drug regimens generally used for less severe hypertension in this clinic, namely, reserpine plus saluretic agents or reserpine, saluretic agents and small doses of hydralazine. The low incidence of side-effects, lack of orthostatic hypotension, simpler titration of dosages, and equivalent frequency of administration (3 or 4 times daily with hydralazine) would seem to contradict replacement of these regimens with methyldopa as the first choice of treatment in most patients with benign hypertension.

Summary

Twenty-four male patients with moderate to severe hypertension were treated with methyldopa for an average period of 9 months (range 2.5 to 22 months). The mean daily dose was 1,390 mg., usually in conjunction with a saluretic agent. Sixteen of the 24 patients maintained a significant reduction of blood pressure. Tolerance was observed in 3 cases. The side-effects were minimal and consisted principally of drowsiness during the initial period of treatment.

Two instances of febrile reactions associated with disturbances in liver function tests were observed. Abnormalities of liver function recurred when methyldopa was reinstituted. In 1 of these patients needle biopsy taken during the acute illness demonstrated toxic injury to liver cells compatible with drug-induced hepatitis.

Methyldopa was compared with guanethidine in 13 patients. Treatment with methyldopa was associated with fewer side-effects than with guanethidine but was not preferred by most patients, largely because of the large number of tablets and greater frequency of dosage required. Orthostatic reduction of blood pressure usually was greater with guanethidine.

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